

**EXHIBIT G**

SIGNIFICANT ACTIVITIES  
UNDERTAKEN BY THE MARKETING APPLICANT  
DURING THE  
IND PHASE  
OF THE REGULATORY REVIEW PERIOD

IND 46,687 Tiotropium Bromide

Date	Submission Type	Abstract
30-Nov-94	ORIGINAL IND SN 000	Quaternary ammonium compound being investigated as long-acting anticholinergic bronchodilator for <u>treatment of patients with reversible airway diseases</u>
08-Dec-94	Agency Contact Report	On 12/8, Dr. Sun of FDA called to get clarification on the recent submission. On 12/9, BIPI confirmed that calculations were present for all inhalation doses and were present in the appendices. Dr. Sun <u>requested table with only the pulmonary doses.</u>
09-Dec-94	Agency Contact Report	FDA called for clinical labels on studies in Germany and Holland.
09-Dec-94	FDA Acknowledgement of Receipt	Submission sent 11/30/94 and received 12/2/94.
12-Dec-94	FAX	Response to call from Dr. Sun of FDA on 12/9/94 regarding clarification of calculations used for determining the theoretical dose to the lung, used for the inhalation studies conducted.
13-Dec-94	Agency Contact Report	Dr. Sun of FDA requested a clarification fo the table faxed to him on 12/12/94.
14-Dec-94	FAX	Regarding 12/13 conversation with FDA, attached updated table containing the theoretical pulmonary doses calculated for the inhalation studies conducted in the rat, dog and mouse.
19-Dec-94	Protocol Amendment: New Investigators SN 001	New Investigators: Prot. # 00921, Drs. Aurerbach, Bode, Campbell, Dunn, Ilowite, Littner, Taskin and
05-Jan-95	Agency Contact Report	FDA sent a fax dated 1/5 to resolve issues on clinical protocol. Outcome of discussions are in BIPI fax to FDA dated 1/6.
05-Jan-95	FAX	From FDA to resolve issues on the clinical protocol.
05-Jan-95	General Correspondence	As requested by FDA enclosed are Fo2 Inhalers #27.1 (RM 1452-2-2), #27.3 (RM 1452-2-3), #27.3 (RM 1452-3-2), 51 capsules.
06-Jan-95	Agency Contact Report	Dr. Sun of FDA called 1/6 and 1/10 to get information on the KCS seen in the dog toxicology
06-Jan-95	FAX	Response to January 5, 1995 Fax from FDA (includes Protocol addendum).
10-Jan-95	FAX	To Drs. Schillings and Bispham of BIGmbH informing them of fax to FDA in which BIPI sent requested labels from the clinical studies conducted in Netherlands (U94-0198) and in Germany (U93-
10-Jan-95	Agency Contact Report	The FDA clinical team met on 1/10 to discuss outcome of their review and they faxed a list of 13 issues. These issues were discussed on 1/11. The outcome of these discussions were faxed to FDA on 1/12. FDA confirmed that this completed all <u>obligations to IND and to allow the initiation of</u>
10-Jan-95	FAX	called Dr. Sun of FDA in response to his calls of 1/6 and 1/10 regarding his request for clarification on the KCS reported in the 5 ug/kg/day dose study #U91-0510 (13-week oral study in dogs), and the absence of KCS in the 4ug/kg/day dose in study #U91-0494 (4-week I.V. study in dogs).
12-Jan-95	FAX	BIPI has provided FDA minutes of telephone conference call to discuss clinical issues presented in facsimile from Drs. Pina and Himmel dated 1/10.

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27-Jan-95	Protocol Amendment: New Investigators SN 002	New Investigator, Prot. #00921, Dr. M. Friedman.
02-Feb-95	FAX	FDA has completed review of IND and BIPI may proceed. IND effective February 2, 1995. FDA requests additional information.
06-Feb-95	FDA Request for Information (rec'd by mail; follow-up of February 2, 1995 Fax)	FDA has completed review of the IND and the study may proceed. The enclosed recommendations and requests for additional information is required.
21-Mar-95	Protocol Amendment: New Investigators SN 003	New Investigator, Dr. Joseph Broughton, "Randomized, Multiple-Dose, Double-Blind, Parallel Group Study to Determine the Optimal Dose of Ba679 BR Inhaled as powder in Patients"
22-Aug-95 31-Aug-95	Agency Contact Report	Called Dr. Sun of FDA to tell him that the ongoing male mouse carcinogenicity study being conducted at BIKG is in week 58 and unexpected mortality is noted at the Mid and High dose levels as included in
04-Jan-96	Agency Contact Report	Drug induced mortality on mouse male repeat carcinogenicity study on-going in Germany
11-Jan-96	Agency Contact Report	BA 679 Two Year Mouse Carcinogenicity Study - Dr. Joe DeGeorge of the FDA (Supervisory Pharmacologist of Oncology), Chairperson the FDA Carcinogenicity Committee called as a follow-up of my conversation with Dr. Joseph Sun (supervisory Pharmacologist of Pulmonary).
23-Feb-96	Agency Contact Report	Dr. S. Tripathi has requested a summary table for PK data for all animals/routes/doses provided in the IND.
19-Mar-96	FAX	PK Table draft outline, and request for a 3/20/96 morning telephone call with Drs. Tripathi and Sun. Table contains summary data already in U91-0236, U91-0491. BIPI asks for FDA feedback of table format and content prior to adding data to other PK
02-Apr-96	FAX	PK Table outline data for animal studies.
11-Apr-96	Agency Contact Report	Informed Dr. Tripathi of FDA the route of administration employed in ongoing mouse carcinogenicity study was via inhalation
16-Apr-96	FDA Request for Information	Request for annual report
25-Apr-96	Annual Report SN 004	Reporting period December 13, 1994 - December 31,
16-Sep-96	FDA Request for Information	Attached is BIPI's correspondence with Dr. J. Sun held during the IND review in December 1994 regarding information on deposition factor for pre-clinical inhalation studies conducted, these data were sent to him on 12/12/94
19-Sep-96	General Correspondence SN 005	Response to FDA fax of 9/12/96: information on deposition factor for pre-clinical inhalation studies conducted
26-Sep-96	Information Amendment: Clinical SN 006	Clinical report, U96-3068
16-Oct-96	Request for Meeting SN 007	Initial request for end of phase II meeting, to initiate scheduling of meeting for the end of November 1996
17-Oct-96	FAX	FAX to Cathy Schumaker: initial request of end-of-phase II meeting
24-Oct-96	Request for Meeting SN 008	Request for End-of-Phase II Meeting Package
24-Oct-96	Response to FDA Comments SN 009	BIPI response to items 1 to 13, pertaining to clinical section. (Tiotropium Powder Inhalation System)

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29-Oct-96	Agency Contact Report	Cathie Schumaker called and said earliest end of phase 2 meeting could be scheduled is 12/3/96 from 3:00 to 5:00, Peter Fernandes will call back FDA to
30-Oct-96	FAX	Telefax from FDA Confirming meeting December 3,
05-Nov-96	Meeting Package SN 010	Pharmacology and toxicology summary pre-meeting package volume 3, volume 1 & 2 submitted 10/24/96, Ser.# 008
20-Nov-96	FAX	FAX to FDA: overall human-pharmacokinetic summary of 6 clinical studies previously submitted to the IND and an outline of human-pharmacokinetic studies underway or planned
20-Nov-96	Meeting Package SN 011	Pharmacokinetic summary, pre-meeting package, Vol 4. This is an information package for Clinical Section and Drug Product CMC. Three additional pharmacokinetic reports of study 205.104 (U94-0776), Study 205.120 (U95-0066), and U96-2136.
22-Nov-96	Agency Contact Report	Dr. Brian Rogers, CMC reviewer requested clarification on differences between Handihaler used in report U96-2266 and that used in report U96-2295
22-Nov-96	Agency Contact Report	FDA internal meeting outcome of end of phase 2
26-Nov-96	FDA Comments	Comments from FDA reviewers for discussion at 12/3/96 meeting
05-Dec-96	FAX	FAX to FDA, copy of daily patient record sheet to address issue #7 for real-time diary-records to be given to the patient
20-Dec-96	Meeting Minutes	End-of-Phase 2 Meeting, held 12/3/96 with FDA, regarding chemistry, preclinical, biopharm, clinical, statistics.
20-Dec-96	Meeting Minutes; FAX	End of Phase 2 Meeting minutes.
14-Feb-97	Protocol Amendment: New Protocol and New Investigators SN 012	New protocol, Prot.# 205.114/205.117, A multiple dose comparison of 18 mcg of tiotropium inhalation capsules and placebo in a one-year, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease (COPD); New Investigators, Drs. Amin Baughman, Blumberg, Briggs, Cary, Casaburi, Craig, DeFruff, Donohue, Friedman, Kane, Hiller, Karpel, Knoper, Levin, Liu, Mahler, Mandel, Miller, Ramsdell, Skatrud, Truitt
14-Feb-97 11-Mar-97	FDA Comments	FDA comments on BIPI comments made at End-of-Phase II meeting including endpoint for QOL analysis, addition of symptoms and activities scores of SGRQ, changes in medication, premature discontinuation, PERFs, PK endpoints.
27-Feb-97	Information Amendment: Clinical SN 013	Clinical report, U96-0240
10-Mar-97	Information Amendment	BIPI's proposal to investigate tiotropium bromide's bronchodilative properties in asthmatic patients
10-Mar-97	FDA Comments SN 014	Response to 3/10/97 general investigative plan & initial protocol for an additional indication other than
11-Mar-97	FDA Comments	Response to BIPI's comments from FDA's comments on end-of-phase II meeting and remaining outstanding issues
02-Apr-97	Meeting Minutes SN 015	Final minutes of end-of-phase 2 meeting of 12/3/96
04-Apr-97	Protocol Amendment: New Investigators SN 016	New Investigators, Drs. Anzueto, Auerbach, Goldman, Prot.#205.114/205.117

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09-Apr-97	Information Amendment: Pharmtox SN 017	Pharmacology/Toxicology reports, U95-0136, U95-0137, U95-0138, U95-0177, U95-0221, U95-0222, U95-0471, U96-2493, U95-0485, U94-0368, U94-
21-Apr-97	Protocol Amendment: Change in Protocol SN 018	Change in Protocol, Prot.# 205.201, revised inclusion criteria
23-Apr-97	Protocol Amendment: New Investigators SN 019	New Investigator; Dr Knoper, Protocol 205.115/205.128.
09-Jun-97	Information Amendment: CMC and Protocol Amendment: New Investigators SN 020	CMC amendment for formulation changes to 4.5 9, 18 & 36 mcg; New Investigator, Dr. Noveck, Prot.# 205.201
10-Jun-97	Annual Report SN 021	Reporting period December 14, 1995 - December 13,
13-Jun-97	Protocol Amendment: New Investigators SN 022	New Investigators, Drs. Berger, Corren, Gross, Lazarus, Noveck, Pearlman, Segall, Storms, Prot.#
16-Jun-97	Protocol Amendment: Change in protocol SN 023	Change in Protocol, Prot.# 205.201, revised inclusion criteria
10-Jul-97	Protocol Amendment: New Investigators SN 024	New Investigators, Drs. Grossman, Snyder, Taylor, Volz, Prot.# 205.201
15-Jul-97	Protocol Amendment: New Protocol and New Investigators SN 025	New protocol, Prot.# 205.132, Study of handihaler flow rater characteristics in patients with COPD; New Investigator, Dr. Chodosh, Prot.# 205.132
17-Jul-97	Protocol Amendment: New Protocol SN 026	New Protocol, Prot.# 205.202, Study to assess the safety and efficacy of patients with moderate to severe asthma who suffer from nocturnal symptoms; New Investigators, Drs. Beamis, Busse, Grossman, Hudge, Israel, Lewis, Nathan, San Pedro, Schenkel, Smith Tashkin Prot # 205.202
21-Jul-97	FDA Comments	Comments on protocol 205.202
12-Aug-97	FDA Comments	Response to 4/9/97 submission regarding embryocidal and fetotoxic activity in preclinical data
03-Sep-97	Agency Contact Report	Inquired on division's concerns regarding flow rate study, protocol # 205.132
29-Sep-97	Protocol Amendment SN 027	Information regarding St. Mary's Questionnaire, randomization. Protocol amendment for 205.202, entitled, The effects of tiotropium in patients with nocturnal asthma.
07-Oct-97	Response to FDA Request for Information	Sent statement from BIPI toxicologist regarding comments of FDA fax of August 12, 1997. Changes will be formally submitted to IND, along with additional rat oral range finding Setment I and III
07-Oct-97	Agency Contact Report	Inform FDA on our response to August 12 fax and on the 2 preliminary oral dose range studies to be submitted shortly to the IND.
07-Oct-97	Protocol Amendment: New Investigators SN 028	New Investigators, Drs. Chervinsky, Martin, Taylor Prot.# 205.202
09-Oct-97	Response to FDA Request for Information SN 029	Toxicology statement to answer FDA questions.
10-Oct-97	Information Amendment: Pharmtox SN 030	Pharmacology, Toxicology amendment providing for 2 additional preliminary rat oral range findings (U90-0539 and U90-0540). Route of administration in man is by inhalation.
24-Oct-97	Response to FDA Request for Information	Responses to FDA fax dated August 12, 1997, regarding 2 preliminary oral dose range studies
05-Nov-97	General Correspondence SN 031	Hard copy of fax sent to Ms. Kuzmik on 11/5/97 provided, fax is in response to FDA discussions on 10/7 & 10/24 regarding supporting historical data on survival following fewer implantations in rats

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06-Nov-97	Agency Contact Report	Dr. Tripathi's receipt of fax regarding historical data.
27-Dec-97	Protocol Amendment SN 032	New Investigator, Dr. Noveck, Prot.# 205.202
14-Apr-98	Annual Report SN 033	Reporting period December 13, 1996 - December 13,
27-Apr-98	Safety Report SN 034	1998-001058/Initial, haematuria
28-Apr-98	Agency Contact Report	Setting up the pre-NDA meeting.
06-May-98	Safety Report SN 035	1998-001058/Follow-up, worsening hematuria
12-Jun-98	Information Amendment: Clinical SN 036	Clinical trial Protocols, Prot.# 205.133 & 205.134.
12-Oct-98	Response to FDA Request for Information	Response to FDA hold designation of 10/1/98, detention of 002/001, entry #996-0421956-0.
27-Oct-98	Protocol Amendment SN 037	New protocols, Prot.# 205.130 and 205.137, A multiple dose comparison of tiotropium inhalation capsules, salmeterol inhalation aerosol and placebo in a six-month, double-blind, double-dummy, safety and efficacy study in patients with chronic obstructive pulmonary disease (COPD), protocol 205.130 a 12 hour pulmonary function test will be conducted and for protocol 205.137 a 3 hour pulmonary function test
12-Feb-99	Safety Report SN 038	1998-001058/Follow-up, hematuria.
04-Mar-99	Request for Meeting	Request for a Pre-NDA meeting, proposed agenda is attached.
05-Mar-99	Protocol Amendment: New Investigators SN 039	New Investigators, Drs. Donohue, Ilowitz, Lapidus, Taylor Ziment, Prot.#205.130; New Investigators, Drs. Enright, Rodarte, Prot.# 205.137.
05-Mar-99	Request for Meeting SN 040	Request for a Pre-NDA meeting. Proposed agenda and estimated duration for each section is attached.
15-Mar-99	Request for Meeting SN 041	Pre-NDA meeting request and meeting package. BI is targeting an NDA submission for tiotropium powder inhalation system in December, 1999. This meeting package contains summary information and specific questions on the topics listed in the proposed agenda.
26-Apr-99	Safety Report SN 042	Follow-up report: 1998-001058. Study 205.127
28-Apr-99	General Correspondence	Drug product samples for pre-NDA meeting. HandiHaler device (lot# 9602001) Placebo Inhalation Capsules (lot# 9602001). Also provided is the list for attendees for the CMC meeting on May 10, 1999 and the general meeting of May 12, 1999.
28-Apr-99	FAX	Enclosed is the cover letter to the package being sent via FedEx which contains drug product samples of the HandiHaler and Placebo Capsules. Also enclosed is the list of attendees for the CMC and General Pre-NDA meeting which will be held in May 10, and 12.
29-Apr-99	Annual Report SN 043	Information amendment clinical - investigator's brochure. Version 6 of the IB dated September 1, 1998 (U92-0551). For the reporting period December 14, 1997 to December 13, 1998.
04-May-99	Information Amendment: Clinical SN 044	12 week portions of the following two phase III clinical reports: U98-3105 and U98-3142.
05-May-99	General Correspondence SN 045	Enclosed is an addendum to the CMC section of the Pre-NDA meeting package for item 5.0 primary packaging material.
06-May-99	FAX	Attendees and room number for pre-NDA meeting for tiotropium on 5/10/99 and 5/12/99.

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20-May-99	Meeting Minutes; General Correspondence SN 046	Tiotropium Br Powder Inhalation System. Copy of BIPi's Pre-NDA Meeting Minutes, CMC & General, held May 10 and May 12, 1999 with FDA. These BI minutes reflect BIs understanding of the agreements and discussions reached during the Pre-NDA
25-May-99	Agency Contact Report	the complete final carcinogenicity study reports can be submitted to the IND for the CAC review and the electronic carcinogenicity datasets can be submitted with the NDA.
18-Jun-99	Meeting Minutes	CMC pre-NDA minutes for 5/10/99 meeting.
29-Jul-99	Protocol Amendment: New Protocol SN 047	BIPI is amending this IND to provide for a new protocol. Enclosed is protocol 205.121 and
02-Aug-99	Meeting Minutes	Pre-NDA industry meeting minutes of 5/12/99 between the division of Pulmonary drug products and
02-Aug-99	Agency Contact Report	Feedback regarding start of protocol 205.121, notify potential delay to NDA.
09-Aug-99	Protocol Amendment: New Investigator SN 048	Enclosed is investigator documentation for new investigators who are conducting studies for protocol 205.121. This protocol was submitted July 29, 1999, Serial No. 047.
27-Aug-99	Agency Contact Report	Tiotropium: FDA acceptability regarding start of protocol 205.121. FDA agreement to review and comment on dyspnea. New MRO Dr. Eugene
01-Dec-99	Protocol Amendment SN 049	This submission provides for Amendment 2 (9/22/99) to Protocol 205.121 to redefine calculation of trapped air volume, to clarify recording of pulmonary function parameters and to adjust time windows as requested by study sites.
17-Dec-99	Protocol Amendment SN 050	New Investigators: enclosed is investigator documentation for Dr. Rodarte who is conducting study 205.121. Also enclosed is investigator documentation for Dr. Zibrack who is conducting
22-Dec-99	Safety Report; FAX	IND Safety report, 1999-002185, adverse events: Tachycardia ventricular.
29-Dec-99	Safety Report SN 051	Initial report, 1999-002185, adverse events: Tachycardia ventricular.
04-Jan-00	Agency Contact Report	General questions on registration strategy for HandiHaler device and on requirements for PAI for HandiHaler.
05-Jan-00	Safety Report SN 052	1999-002185, adverse events: Tachycardia
07-Jan-00	Information Amendment SN 053	Pharmacology/Toxicology: BIPI is amending the IND to provide for 16 nonclinical reports. U97-2730, U98-2292, U98-2386, U98-2850, U98-2851, U98-2879, U99-0166, U99-0167, U99-0205, U99-1322, U99-1336, U99-1347, U99-1349, U99-1357, U99-1358.
10-Jan-00	FAX	Submissions which need Serial No. corrections. Ser.# 049 should be 050 and Ser.# 050 should be 051.
10-Jan-00	Information Amendment SN 054	BIPI is amending the referenced IND to provide for the following clinical reports: U98-2067 and U99-
10-Jan-00	Information Amendment SN 055	BIPI is amending the referenced IND to provide for an updated Investigators Brochure.
25-Jan-00	7 Day Alert; Safety Report; FAX	1999-002158, adverse events: Sudden death.
26-Jan-00	IND Safety Report SN 056	Initial report: 1999-002158, adverse events: Sudden death.

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23-Feb-00	Protocol Amendment SN 057	BIPI is amending this IND to provide for a new protocol. Enclosed is a Phase IIIb protocol (205.218) entitled, "The effect of tiotropium therapy on airway diameter in patients with COPD (A randomized, double-blind, placebo controlled, parallel group
29-Mar-00	Information Amendment SN 058	BIPI is amending the above referenced IND to provide for the following clinical initial 13-week study reports. U98-2142, U98-2105, U99-0060, U99-
02-May-00	Information Amendment SN 059	Clinical: BIPI is amending the IND to provide the full one-year reports (U99-2169, U99-2170, U00-2112 and U00-2114)
19-Jun-00	FAX Request for Meeting	Request for Type B Clinical meeting, attached is the fax copy of the cover letter on BI's request for a Type B Clinical meeting and the pre-meeting information package.
19-Jun-00	Request for Meeting SN 060	Request for a Type B Clinical Meeting, BIPI is requesting a meeting to review the outcome of the Phase III studies, and in particular to agree on the proposed analysis and presentation of these data to allow appropriate label claims for dyspnea and
26-Jun-00	IND Annual Report SN 061	Reporting period of December 14, 1998 to December 12, 1999 also contains the Investigator's Brochure (U92-0551 Version 7).
07-Jul-00	Information Amendment:CMC SN 062	BIPI is amending this IND to provide for information related to the testing of clinical supplies, enclosed are updated testing specifications for the active and placebo capsules.
13-Jul-00	Safety Report SN 063	Follow-up, 1999-002185, adverse events: Tachycardia ventricular.
02-Aug-00	Protocol Amendment: New Investigator	New Investigator Dr Johnson 205.121
14-Aug-00	Fax Meeting with Health Authority Corresp	Telefax of 7-24-00 meeting minutes
22-Aug-00	Fax - IND Prot Amend - Change in Protocol	Fax: Notification of forthcoming submission, draft protocol amendment for 205.120 and 205.127 to secure a second indication for relief of dyspnea
22-Aug-00	Protocol Amendment: Change in Protocol SN 065	Draft Prot amend: Proposed change in Protocol 205.120 and 205.127 second indication for relief of
20-Aug-00	General Correspondence	BI sent a Fax regarding sending of 7 desk copies to attention of David Hilfiker, FDA for submission dated 8/22/00
20-Aug-00	Fax - General Correspondence	Fax to David Hilfiker, FDA
11-Oct-00	Fax - General Correspondence	FDA Fax comments regarding SN 065 concerning protocol amendments 205.120 and 205.127 and
11-Oct-00	General Correspondence - Protocol Amendment: Change in Protocol	letter from FDA with comments regarding SN 065 and the new NDA
12-Oct-00	Protocol Amendment: New Protocol SN 066	Prot Amend: New protocol and investigator 502.223
13-Oct-00	Protocol Amendment: Change in Protocol SN 067	Final Protocol Amendment (205.120 and 205.127)
13-Oct-00	Fax - General Correspondence - Protocol Amendment	Telefax 10/13/2000 re protocol amendment
20-Oct-00	Information Amendment: Clinical SN 069	Clinical updated IB (u92-0551) Version 8
20-Oct-00	Protocol Amendment: Changes in a Protocol, Protocol Amendment: New Protocol SN 068	Change in protocol 205.224 amend #1

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15-Nov-00	Protocol Amendment: Change in Protocol and New Investigator SN 070	Change in Protocol 205.223 New Investigator - Dr. Richard Light
30-Nov-00	Protocol Amendment: New Investigator SN 071	Protocol Amendment 205.218 New Investigators
01-Dec-00	Agency Contact Report	Pharm/Tox review not yet initiated and Executive CAC meets weekly as needed
07-Dec-00	Agency Contact Report	Division informed of final carcinogenicity report being submitted with form request for review by
08-Dec-00	Information Amendment: CMC SN 072	Updated Testing Specification 156 0018 998-06 and Testing Specification 156 0018 998-08
15-Dec-00	Information Amendment: Pharmtox SN 073	3 Carcinogenicity reports
05-Jan-01	Safety Report SN 074	Written follow-up no. 3 for safety report 1999-003185 was submitted.
12-Jan-01	Agency Contact Report	Follow-up status of Dec. 15, 2000 submission (SN 073) Exec. CAC meets every week as needed.
25-Jan-01	Agency Contact Report	Status of FDA on-going review of Carcinogenicity reports; FDA requests electronic data of SAS datasets, BIPI requests for potential FDA
07-Feb-01		consultation on extent of data needed electronically.
05-Mar-01		
23-Feb-01	Protocol Amendment: New Protocol and Change in Protocol SN 075	New protocol 205.230 and Amendment 1 for protocol 205.230 were submitted.
06-Apr-01	Annual Report SN 076	Reporting period 12/14/99 to 12/13/00
09-Apr-01	Protocol Amendment: New Investigator SN 077	New Investigators for 205.218, 205.223, and 205.234
19-Apr-01	Protocol Amendment: Change in Protocol SN 078	Amendment 3 for protocol 205.218 was submitted.
03-May-01	Agency Contact Report	FDA phoned requesting clarification on Amendment 3 to Protocol 205.218 submission 4/19/01 SN 078
09-May-01	Agency Contact Report	FDA phoned requesting clarification on Amendment 3 to Protocol 205.218 submission 4/19/01 SN 078
12-May-01	Agency Contact Report	BIPI phoned eSub Coordinator to obtain feedback on specific strategies for planned NDA.
22-May-01		
23-May-01		
25-May-01	Protocol Amendment: Change in Protocol and New Investigator SN 079	Amendment 2 for protocol 205.230 was submitted. Additionally New Investigators for 205.230 were submitted.
29-May-01	Agency Contact Report	BIPI phoned eSub Coordinator on FDA's preference eNDA section TOC should be more detailed than folder structure
30-May-01		
12-Jun-01	Agency Contact Report	Contacted FDA to obtain User Fee Number (4162) and NDA Number (21-395)
13-Jun-01	FDA General Regulatory Letter	Fax from FDA with NDA number and User Fee
14-Jun-01	Agency Contact Report	BIPI phoned D. Hilfiker with questions regarding Spiriva Training Kit
15-Jun-01	Agency Contact Report	BIPI phoned FDA and confirmed format and content of Safety section of labeling
03-Jul-01	Health Auth Comments Pharmtox SN 080	Response to FDA request for information on carcinogenicity datasets for 3 studies (U98-2726, U98-2727, U99-1464)
03-Jul-01	Protocol Amendment: Change in Protocol SN 081	Protocol Amendment, amendment 1, 2 and 4. Amendment 1 and 2 were inadvertently never submitted and amendment 4 clarifies a question received by the agency about amendment 3.

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06-Jul-01	Protocol Amendment - Change in Protocol SN 082	Protocol amendment 2 for protocol 205.222 was submitted. This amendment changed inclusion criteria age to extend from less than or equal to 70 to be less than or equal to 75.
20-Jul-01	Agency Contact Report	FDA contacted regarding the submission of the Tradename for evaluation. FDA informed of the upcoming protocol amendment submission (Serial No. 082) for protocol 205.266 which included a proposal not to collect non-serious adverse events.
23-Jul-01	Protocol Amendment: New Protocol SN 082	Protocol Amendment for new protocol 205.266 Request for FDA confirmation on acceptability of only collecint SAEs (i.e. non-serious adverse events are not collected). This is a Phase IIIb VA study with exacerbation endpoints.
26-Jul-01	Agency Contact Report	FDA feedback on Protocol 205.266 (SN 082) provided. Review of the carcinogenicity datasets (SN 080) is ongoing. Format for stability data provided. Update of the electronic submission proposal will be
02-Aug-01	Agency Contact Report	FDA contacted regarding IT related issues for the electronic submission. FDA indicated version 8.5 with 35/70 DLT tape should be used. Files should not be compressed per Randy Levin - FDA.
14-Aug-01	FDA FAX Comments or Request for Information	FDA provided feedback regarding protocol 205.266 (VA study) which included a proposal to not collect non-serious adverse events. The decision to collect or not collect non-serious AE data is BI's. Info for formatting electronic stability datasets provid
14-Aug-01	Protocol Amendment: New Investigator SN 084	New Investigators for 205.120: Irwin, Jimenez, Casaburi, MacIntyre
22-Aug-01	General Correspondence SN 085	BI requested FDA for a formal evaluation of the tradename SPIRIVA. No back-up names were submitted. SPIRIVA has been registered in the U.S.
25-Sept-01 26-Sept-01	Agency Contact Report	CDER esub coordinator contacted regarding eNDA 21-295. Reports should only be included once in the eNDA. Reports can be listed multiple times in a TOC. Preference that bookmarks in pdf should be
26-Sept-01	Protocol Amendment: New Investigator and New Protocol SN 086	Protocol Amendment No. 1 and New Investigators for 205.266, Drs. Cooper, Farber, Cote, Fulambarker, Gonzalez_Rothi, Habib, Krumpe, Paulson, Piquette, Rice, Sethi, Sharafkhaneh, Young
01-Oct-01	Agency Contact Report	OPDRA indicated they did not have enough information to evaluate our tradename proposal (22Aug01; SN 082). A draft package insert is minimally needed and ultimately color mockups
05-Oct-01	IND Safety Report SN 087	Safety Update Medwatch form 2001-NB-TIO22
08-Oct-01	Information Amendment: Clinical SN 088	(Asthma) Clinical Reports U98-2174, U98-274, U99-1019
08-Oct-01	General Correspondence SN 089	General Correspondence Request for Pediatric Waiver for NDA 21-295
11-Oct-01	Agency Contact Report	BIPI phone FDA Document Control Room to obtain a DMF number; however, FDA does not pre-assign numbers
15-Oct-01	Agency Contact Report	It is possible to send a test esub DLT tape to CDER's Electronic Document Room
15-Oct-01	Agency Contact Report	It is possible to send a test esub DLT tape to CDER's Electronic Document Room

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17-Oct-01	Protocol Amendment: New Investigator SN 090	Protocol Amendment - New Investigators 205.266 Drs Gross, Shahbaz-Hasan
18-Oct-01	Agency Contact Report	CDER supports arial and times new roman fonts for an electronic submission.
18-Oct-01	IND Safety Report SN 091	IND Safety Report - Follow-up Report 2001-NB-
22-Oct-01	Agency Contact Report	Submission of the DRAFT package insert will allow the assessment of the Tradename to continue
23-Oct-01	Agency Contact Report	The (paper) review copy does not need to include clinical study report appendices 16.1.3 to 16.4 as defined in the ICH Clinical Study Report. Review Copy for Statistical Reviewer can be the same as the Review Copy for the Medical Reviewer.
23-Oct-01	Health Auth Comments Labeling SN 092	The Draft Package Insert (24Sep01) version was submitted in order that the assessment of the Tradename, SPIRIVA, can continue
25-Oct-01	Agency Contact Report	The test tape will be processed under the same procedures and on the same systems that would be used if it was the official submission. At completion of test, data will be removed from EDR system.
26-Oct-01	General Correspondence	A test esub DLT tape was submitted to CDER's electronic document room (EDR). The tape contained pharmtox, crt and crf data and is to support the upcoming SPIRIVA eNDA.
29-Oct-01	Agency Contact Report	The test esub DLT tape submitted on October 29, 2001 was successfully loaded by FDA's Electronic Document Room.
29-Oct-01	IND Safety Report SN 093	IND Safety Report Follow-up #2 2001-NB-TIO32
05-Nov-01	Agency Contact Report	The Review Copies for the upcoming eNDA were confirmed. There is no update regarding the FDA's evaluation of the Tradename, SPIRIVA.
12-Nov-01 14-Nov-01	Agency Contact Report	For the upcoming eNDA, Items 19 (Financial Information) and 20 (Other) should be included in one folder called other". "
12-Nov-01 14-Nov-01 15-Nov-01 16-Nov-01	Agency Contact Report	The eSub Coordinator recommended following the current eSub Guidance for the CMC section, but if we want to use the CTD format we should follow the recently published draft ICH/CTD general considerations guidance until the ICH eCTD guidance is completed.
14-Nov-01	Agency Contact Report	The IND submission for the Pediatric Waiver Request should be cited in the NDA cover letter. There is no update on FDA's evaluation of the carcinogenicity studies. The Division wants the non-annotated version of the labeling to be provided as
16-Nov-01	Agency Contact Report	The FDA statistician is still reviewing and analyzing the tumor datasets. The Division's report has not yet been sent to the CAC committee.
19-Nov-01	Protocol Amendment: New Investigator SN 094	New Investigators 205.266 Drs. Friedman, McCormick, Shigeoka, Gottlieb, Kuschner and
19-Nov-01 27-Nov-01 28-Nov-01	Agency Contact Report	ESub Coordinator was contacted. Subfolders should not be created for labeling components. All files should be included directly in the labeling folder. Each labeling component should be a separate pdf file in the labeling folder.
20-Nov-01	Agency Contact Report	Address for the NDA field copy was confirmed.

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28-Nov-01	Agency Contact Report	The current Project Manager will be leaving on December 7, 2001. The new Project Manager will be Tony Zecola.
27-Nov-01 28-Nov-01	Agency Contact Report	CDER's eSub Coordinator was contacted to answer a question about the method validation section.
27-Nov-01 28-Nov-01	Agency Contact Report	Esub Coordinator was contacted. A workaround for indexing folders with large amounts of data was obtained. It is acceptable to create 2 crf tocs and associate 1 index file (.pdx) with each or create a third crf toc which points to the second and third
07-Dec-01	General Correspondence SN 095	An updated electronic submission proposal for the SPIRIVA eNDA was submitted.
10-Dec-01	Agency Contact Report	Notify FDA Document Control Room of SPIRIVA electronic submission and 142 review copies
10-Dec-01	General Correspondence	The User Fee of \$309,647, along with FDA Form 397, was submitted to Mellon Bank. The User Fee for SPIRIVA NDA 21-395 is 4162.
14-Dec-01	Information Amendment: Clinical SN 097	The updated investigator's brochure (U92-0551; Version 9, dated) was submitted.
14-Dec-01	Protocol Amendment: New Investigator and Change in Protocol SN 096	Protocol Amendment: New Investigators for 205.223 (Celli), 205.230 (Diamond) and 205.266 (Anzueto) and Change in Protocol 205.230 (Amendment 3)

SIGNIFICANT ACTIVITIES  
UNDERTAKEN BY THE MARKETING APPLICANT  
DURING THE  
NDA PHASE  
OF THE REGULATORY REVIEW PERIOD

NDA 21-395 Spiriva HandiHaler  
(tiotropium bromide inhalation powder)

Date	Submission Type	Abstract
12-Dec-01	Original Application	Original NDA 21-395 submission for SPIRIVA (tiotropium bromide inhalation powder) on December 12, 2001. This was a complete electronic NDA.
12-Dec-01	General Correspondence	Peggy Hair in the FDA Document Room was notified the SPIRIVA NDA will arrive on December 13th.
12-Dec-01	FAX	A Fax of the NDA 21395 cover letter was sent to the FDA Project Manager, Tony Zecolla to alert him of its arrival. The NDA shipment consists of one DLT tape and 143 volumes for the paper review copy. This is contained in 16 boxes.
12-Dec-01	NDA sent to Field	The NDA field copy cover letter was submitted to Ms. Irma Rivera along with volumes 1 through 12 (paper review copy versions) from NDA 21395
13-Dec-01	General Correspondence	The first page of the NDA cover letter was stamped on 13Dec01 by the FDA document room.
14-Jan-02	Agency Contact Report	An update on the FDA's evaluation of the Tradename (SPIRIVA) was requested.
4-Feb-02	Agency Contact Report	FDA contacted regarding 45 day review use of trade name possible advisory committee meeting
4-Feb-02	Agency Contact Report	The CDER esub coordinator was contacted for guidance on future electronic submissions to the SPIRIVA NDA 21-395. Hyperlinks across submissions are not needed. The folder/file structure for the 4 month safety update is provided in the esub guidance.
11-Feb-02	Agency Contact Report	45 Day review and potential Advisory Committee Meeting
12-Feb-02	Agency Contact Report	Official filing date for the SPIRIVA NDA is 11Feb02. The Project Manager would give no specifics, but indicated we could make assumptions regarding the filing of the NDA since we had not heard anything negative. The 4Feb02 request (NDA Vol1) is cancelled.
21-Feb-02	Agency Contact Report	FDA request for copy of Application Summary and Phase III Pivotal Studies Table listing investigators and site, number of patients enrolled and completed, and number of protocols in Phase III program
22-Feb-02	Response to FDA Comments or Request for Information	Response to FDA Request for Information from H. W. Ju, M.D., FDA, on February 21, 2002 for copy of Application Summary and Phase III Pivotal Study Tables listing investigators and sites and number of protocols in Phase III program
28-Feb-02	Response to FDA Comments or Request for Information	Response to FDA request of February 21, 2002 to E. Lyons request number of patients at each site for primary studies
1-Mar-02	Agency Contact Report	FDA Request for Information to assist in potential clinical site audit
5-Mar-02	Agency Contact Report	DSI can be given access to an eNDA. DSI requests can be submitted electronically if listed in Public Docket 92S-251 or the esub Guidance. For information requested outside of 21CFR314 one needs to decide if paper or electronic is appropriate.
5-Mar-02	Agency Contact Report	FDA Request for follow-up Clinical Site Audit Information
5-Mar-02	Agency Contact Report	FDA discussion regarding PADAC, NDA Letter, Drug Product Samples, Respimat FDA feedback

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7-Mar-02	Agency Contact Report	With an eNDA original submission, subsequent submissions can be paper or electronic format. The top level folder for all electronic submissions is the NDA number. Organization of all esubs should follow 356h/esub guidance.
7-Mar-02	Agency Contact Report	With an eNDA original submission, subsequent submissions can be paper or electronic format. The top level folder for all electronic submissions is the NDA number. Organization of all esubs should follow 356h/esub guidance.
7-Mar-02	FDA Acknowledgment of Receipt	Fax from FDA dated March 7, 2002 Acknowledgment of Receipt for SPIRIVA NDA 21395
7-Mar-02	FDA Comments or Request for Information	FDA Fax requesting information to assist in their review of NDA 21395
7-Mar-02	FDA Acknowledgment of Receipt	FDA acknowledgment of receipt for SPIRIVA dated 01Dec12 received 01Dec13
18-Mar-02	Response to FDA Comments or Request for Information	Response to Dr. Ju's (Scientific Investigations) Request for Information on March 5, 2002. Data for Dr. James Donohue Center 10 Study 105.114/205.117 was provided.
18-Mar-02	Response to FDA Comments or Request for Information	Response to FDA Request for Information from Dr. Ju on March 5, 2002 requesting information from Dr. Lapidus site 36 conducting study 205.130
18-Mar-02	Response to FDA Comments or Request for Information	Response to FDA Request for Information from Dr. Ju on March 5, 2002 requesting information on Dr. Donohue's site 33 for study 205.130
18-Mar-02	Agency Contact Report	ACR regarding e-mail to Dr. Ju at FDA with 3 site cover letters to be included in March 18, 2002 submission
19-Mar-02	Response to FDA Comments or Request for Information	Response to FDA Request of February 4, 2002 Tony Zeccola requested samples of HandiHaler device and blister cards as Reviewer Aids"
25-Mar-02	Response to FDA Comments or Request for Information	Partial Response to FDA Request for Information dated March 7, 2002 from Tony Zeccola Clinical and Statistical Questions 2-4
25-Mar-02	Response to FDA Comments or Request for Information	Fax cover letter of submission Response to FDA Request for Information dated March 25 2002 to Tony Zeccola
25-Mar-02	Agency Contact Report	FDA contacted Peter Fernandes regarding missing pages in original NDA submission
28-Mar-02	Agency Contact Report	FDA indicated the entire 3/25/02 submission should be resubmitted as the majority of the xpt files could not be opened. The FDA wants to receive pdf files rather than word and also pdf files of the cover letter and 356h.
2-Apr-02	Response to FDA Comments or Request for Information	Replacement Submission for Response to FDA Request for Information dated March 25, 2002. A partial response to FDA's March 7, 2002 Request for Information. Questions 2, 3 and 4 submitted. Data sets (xpt) files submitted could not be opened
3-Apr-02	General Correspondence	Fax to Tony Zeccola regarding 02Apr02 CD-Rom Resubmission of 25Mar02 RIR
3-Apr-02	General Correspondence	Fax to Tom Selnekovic at FDA CDER Electronic Document Room regarding CD-Rom for 02Apr02 Resubmission of 25Mar02 RIR
8-Apr-02	Agency Contact Report	FDA indicated that the Dummy" name was fine and the xpt files opened"

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12-Apr-02	Response to FDA Comments or Request for Information	Complete Response to FDA Request for Information 07Mar02 CMC Question 1 and 25Mar02 telephone contact regarding missing page from report U99-3169 clinical study 205.117
12-Apr-02	Agency Contact Report	Dr. Kaplan asked Tony Zeccola for alternate date to September 11 PADAC Meeting. Date not set by FDA yet. When letter comes, we can ask for date change. He also want to know issues to be discussed.
18-Apr-02	Amendment to Unapproved NDA	4 month safety update for SPIRIVA (tiotropium bromide) NDA 21-395
13-May-02	Agency Contact Report	FDA information that hyperlinks wouldn't open on 4th Month Safety Update submission of 4/18/02. Was paper not electronic.
14-May-02	Response to FDA Comments or Request for Information	Response to Dr. Ju's request of April 24, 2002 regarding clarification of PFT data
22-May-02	Agency Contact Report	BIPI request to change PADAC mtg date, face-to-face to decide critical issues for PADAC mtg, possible packaging material changes for commercial launch in US
28-May-02	General Correspondence	FDA sent invoice for adjusted User Fee
14-Jun-02	General Correspondence	BIPI sent payment for Annual Product and Establishment fees for 2002
17-Jun-02	Agency Contact Report	PADAC Meeting Date September 6 and request for pre-PADAC meeting
19-Jun-02	Amendment to Unapproved NDA	Updated Annotated Package Insert and remove reference to secondary outcomes of exacerbations frequency, health related QOL and rescue beta2 agonist use. Requesting formal PADAC preparatory meeting.
19-Jun-02	Response to FDA Comments or Request for Information	FDA Request for Clinical Information
19-Jun-02	Amendment to Unapproved NDA	Amendment to Pending NDA; Meeting Request; Updated Annotated Package Insert
19-Jun-02	Agency Contact Report	Discussion with Topper and Zeccola regarding PADAC date 9/6, labeling amendment, pre-PADAC meeting request
21-Jun-02	General Correspondence	No pre-PADAC meeting per FDA but will address key issues
25-Jun-02	General Correspondence	Fax to Tony Zeccola re tele on 21June2002 re FDA interactions to clarify issues PADAC prep. BI amend NDA to remove ref secondary claims for exacerbation, health-related QOL and rescue beta2 agonist. Study 205.131 include key outcomes support dyspnea
27-Jun-02	General Correspondence	Table on SPIRIVA FDA Tacking List for NDA 21395
1-Jul-02	Agency Contact Report	BI had the opportunity to unofficially ask Dr. Brian Rogers, FDA Review Chemist assigned to SPIRIVA, about his review of the NDA. Two positive comments; well written and hyperlinking is easy to work with.
8-Jul-02	FDA Comments or Request for Information	Fax from FDA Dr. Ju regarding data verification tables Visit 9 for Study 205.130 Dr. Donohue Center 33
8-Jul-02	General Correspondence	Call from Dr. Ju regarding Donohue 483 form and Magnitude of effort and Magnitude of task followed by fax and response by fax and submission #10
9-Jul-02	General Correspondence	Ref to tele call with Mr. Zeccola on 21June2002 reg FDA interactions with clarification of issues on PADAC preparation. Remove secondary claims for exacerbation, health related QOL and rescue beta2 agonist. Study 205.131 key outcomes in support dyspnea

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11-Jul-02	Response to FDA Comments or Request for Information	Fax to FDA Dr. Ju re 483 response from Dr. Donohue and entries for Magnitude of Effort and Task data was accurately captured in CFRs; however, error occurred in study report
16-Jul-02	FDA Comments or Request for Information	Response to FDA Fax Tony Zeccola 19 June 02 reg studies 205.114/205.117 and 205.115/205.128 patients measure FEV values at home; when were the ECGs obtained and no. of patients who reached peak FEV1 at each post-dosing time
16-Jul-02	Response to FDA Comments or Request for Information	Fax to FDA Dr. Ju re 483 response from Dr. Donohue and entries for Magnitude of Effort and Task data was accurately captured in CFRs; however, error occurred in study report
17-Jul-02	FDA Comments or Request for Information	Fax from Mr. Zeccola requesting impurity profile of tiotropium used in nonclinical testing.
18-Jul-02	Response to FDA Comments or Request for Information	Fax to Mr. Zeccola regarding telephone conversation on July 17, 2002 concerning amendments to 205.131. Also attached FDA Tracking List
19-Jul-02	FDA Comments or Request for Information	Five questions from Dr. Chowdhury regarding Study 205.131. Questions pertaining to exercise parameters; primary efficacy variable; endurance time at Day 21; differences in treatment effects on test days 42 and 21; list of protocol submissions
22-Jul-02	FDA Comments or Request for Information	Fax from Dr. Chowdhury requesting number of pregnancies that occurred during clinical studies and outcome of pregnancies
22-Jul-02	General Correspondence	Letter from FDA MaryBet Lopez to pre-announce an inspection at Infracor GMBH, Marl, Germany. Scheduled for September 5-6, 2002
24-Jul-02	Response to FDA Comments or Request for Information	BI provided a complete response to FDA's July 19, 2002 request for information regarding pregnancies in clinical trials.
24-Jul-02	Response to FDA Comments or Request for Information	Response to FDA, Kimberly Topper, request for Listing of Investigators submitted in NDA 21395
25-Jul-02	Response to FDA Comments or Request for Information	A complete response to FDA's July 17, 2002 fax was provided. This was a request for the impurity profile of the tiotropium used in nonclinical testing.
25-Jul-02	General Correspondence	FDA pre-announcement of PAI at RPC and DMV
25-Jul-02	Response to FDA Comments or Request for Information	Response to FDA REquest for Information Fax from FDA 2002-07-19 from Dr. B. Chowdhury requesting information on Study 205.131
25-Jul-02	General Correspondence	FDA pre-announcement of PAI at RPC and DMV
26-Jul-02	FDA Comments or Request for Information	This submission provided a response to the FDA Field Investigation's fax of July 22, 2002 regarding an FDA inspection at Infracor. This submission included a signed confirmation from Infracor for the proposed inspection date and hotel information.
26-Jul-02	Fax	Fax from FDA asking for combined data discussing heart rate changes
26-Jul-02	General Correspondence	FAX 7-26-02 to FDA regarding site inspection of GMBH scheduled for 9/5-6, 2002
26-Jul-02	Fax	Fax to FDA 7-26-02 regarding 7/24 and 7/25/02 Submissions sent covering pregnancy, 205.131, impurity profile question, and investigators list
30-Jul-02	General Correspondence	Confirmation from Ingelheim and Biberach that proposed dates for respective PAI is acceptable. Hotel confirmation included.

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31-Jul-02	Response to FDA Comments or Request for Information	Response to FDA Request for Information Fax dated 26July2002 requesting shift tables indicating number and percent of patients exhibiting specific increase in heart rate at each test day. Provide increases of 5, 10, 15 and 20 beats per minute
31-Jul-02	Fax	Fax to FDA regarding 8/2/02 Telecon to discuss 205.131
2-Aug-02	Response to FDA Comments or Request for Information	This submission responded to FDA Field Investigation's fax of 25Jul02 which pre-announced inspection at RPC Formatec in Mellrichstadt, Germany. A signed letter of confirmation from RPC regarding the proposed inspection dates of 23-27Sep02 was included.
2-Aug-02	Agency Contact Report	Clarification on several issues related to the Pre-approval Inspections at RPC (manufacturer of the HandiHaler device) and DMV International (lactose manufacturer) was requested from the Division of Field Investigations.
2-Aug-02	Agency Contact Report	Telecon with FDA 8-2-02 regarding 205.131
5-Aug-02	Fax	Fax to FDA listing 8-2-02 Telecon participants
6-Aug-02	General Correspondence	Pulmonary-Allergy Drugs Advisory Committee Meeting Briefing Package for September 6, 2002
6-Aug-02	General Correspondence	A copy of the August 6, 2002 cmc amendment (submission #16) was submitted to the FDA field office.
6-Aug-02	Response to FDA Comments or Request for Information	CMC Amendment for the 24-month Stability Report as requested by FDA on June 28, 2002. Includes stability dataset
9-Aug-02	Response to FDA Comments or Request for Information	This submission responded to the FDA Field Office fax of July 25, 2002 which announced a pre-inspection at DMV International in Veghal, The Netherlands on October 16-22, 2002. Hotel information and contact information was provided as requested.
12-Aug-02	Response to FDA Comments or Request for Information Field Copy	This submission responded to the information request of August 02, 2002 from Ms. Rivera in which she requested BI to submit another complete copy of the original NDA field copy.
14-Aug-02	Fax	Fax to Zeccola citing e-mail pdf versions of two references
14-Aug-02	FDA General Regulatory Letter	The FDA Int'l Operations Group has cancelled the inspection at RPC Formatec. A replacement pre-approval inspection is schedule for Institut Fresenius for September 23-24, 2002.
15-Aug-02	Agency Contact Report	Feedback from irma Rivera regarding the inspectors and inspections at RPC and DMV. Inspection at RPC cancelled, replaced with inspection at Institute Fresenius
16-Aug-02	Meeting with Health Authority Corresp	FDA provided, via email, their briefing document for the 06Sep02 Pulmonary & Allergy Drugs Advisory Committee which will discuss NDA 21395 (SPIRIVA) for the treatment of bronchospasm and dyspnea associated with COPD.
20-Aug-02	Agency Contact Report	Feedback from Lourdes Valentin regarding dates for PAI at Institute Fresenius
22-Aug-02	Response to FDA Comments or Request for Information	BI replied to the August 22, 2002 fax from the FDA Field Investigation Office. A signed letter from Institut Fresenius agreeing to the inspection dates of October 21-22, 2002 was included.
22-Aug-02	FDA General Regulatory Letter	FAX rec'd from FDA confirming inspection of Institut Fresenius, Taunusstein, Germany. Inspection will determine testing of finished dosage following FDA GMP. Proposed date of inspection Oct 21-22, 2002.
25-Aug-02	Agency Contact Report	Feedback from lourdes Valentin re Inspector Kovacs travel.

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27-Aug-02	General Correspondence	Mr. John White, FDA Field Investigator called for Eileen Wyka regarding upcoming inspection to BI Ingelheim and Biberach the week of September 9th. Mr. White will bring a chemist along. Mr. White requested two translators available.
27-Aug-02	Agency Contact Report	Feedback from Inspector John White re PAI at Ingelheim and Biberach
3-Sep-02	Agency Contact Report	Cancellation of PAI at Infracor
6-Sep-02	Meeting with Health Authority Corresp	FDA's overheads and other meeting information from The Pulmonary and Allergy Drugs Advisory Committee. The PADAC was held on September 6, 2002 for the SPIRVA NDA 21395.
6-Sep-02	Meeting with Health Authority Corresp	BI's primary presentation to the September 06, 2002 Pulmonary and Allergy Drugs Advisory Committee Meeting.
6-Sep-02	Agency Contact Report	FDA questioned PADAC on safety issues, FDA commented on bronchodilator effect and benefit of dyspnea relief
13-Sep-02	Agency Contact Report	Information regarding rescheduling of PAI at Infracor
17-Sep-02	Agency Contact Report	The esub coordinator was contacted regarding advice on preparing an electronic submission for labeling.
18-Sep-02	FDA Comments or Request for Information	This submission provided a complete response to FDA's request for the June 19, 2002 labeling in an electronic format. This was a complete electronic submission with review aids in the review copy.
18-Sep-02	FDA General Regulatory Letter	FAX from FDA Irma Rivera, Program Specialist, pre-announce an inspection of Infracor GmbH in Marl, Germany on October 11, 2002. Requesting BI assistance in obtaining hotel arrangements. FDA is responsible for paying all lodging and incidental expenses.
24-Sep-02	Response to FDA Comments or Request for Information	Response to FDA Request for Information related to the number of subjects exposed to study drug while enrolled in clinical trials
24-Sep-02	Response to FDA Comments or Request for Information - Fax	Fax to Zeccola that submission RIR clinical trials being sent
25-Sep-02	Response to FDA Comments or Request for Information	Response to FDA Request for Information - remove statement to the best knowledge and belief of the undersigned" to Item 16 Debarred Persons"
25-Sep-02	Response to FDA Comments or Request for Information	Asking verification of wording and then submission would be sent - debarment statement
25-Sep-02	Agency Contact Report	Feedback re PAI at DMV International
25-Sep-02	Agency Contact Report	Request for FDA comments on labeling and potential Phase IV commitments as recommended at PADAC on 9-6-02
2-Oct-02	Labeling	This submission provided a labeling amendment in response to the BI/FDA tcon held on 25Sep02. The 02Oct02 version of the package insert was included. This was a complete electronic submission.
2-Oct-02	Agency Contact Report	Labeling Amendment containing cover letter as pdf and history and proposed labeling as word files were sent to Mr. Zeccola by secured e-mail
10-Oct-02	Labeling	FDA proposed labeling of October 10, 2002. Response to the BI submission of October 2, 2002.

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11-Oct-02	Agency Contact Report	Telecon with FDA regarding delay in action letter scheduled to be sent 10-11-02 to allow for more review and additional foreign site inspections
17-Oct-02	Fax	Fax to Zeccola with copy of fax to Meyer on Labeling inclusion request for salmeterol data
17-Oct-02	Fax	Request from Marty Kaplan to Bob Meyer to include salmeterol data in labeling
18-Oct-02	Agency Contact Report	e-mails to agency for labeling discussion and telecon set-up
21-Oct-02	Agency Contact Report	FDA feedback on preclinical toxicology labeling and calculation issues
25-Oct-02	Fax	Fax from FDA regarding pharmacology/toxicology issues
29-Oct-02	Agency Contact Report	CDER's esub coordinator was contacted regarding the approach for responding to an action letter with a complete electronic submission.
31-Oct-02	Health Auth Comments CMC	FDA questions to RPC DMF for the HandiHaler
31-Oct-02	Health Auth Comments CMC	FDA comments to RPC Type III DMF 15696 for the HandiHaler device.
19-Nov-02	Labeling	This submission responded to FDA's October 10, 2002 correspondence by providing the 19Nov02 version of the proposed package insert and patient instructions for use. This submission is a complete electronic submission.
19-Nov-02	Fax	Fax to Zeccola regarding 4-week inhalation study for primary degradation products with substantiating documentation from 1999 FDA's Kearny Dunn
27-Nov-02	Response to FDA Comments or Request for Information	SPIRIVA Toxicology qualification degradants/impurities
3-Dec-02	Agency Contact Report	FDA action letter - CMC review completed, site inspection okay, will hold up on labeling as review not completed by agency, 13-week tox exemption under discussion at agency - letter should come 12/13
13-Dec-02	Fax	Fax with Telecon information for 12/16/02 TC between Tony Zeccola and Peter Fernandes regarding status of action letter for SPIRIVA
13-Dec-02	Agency Contact Report	Status of FDA action letter - late due to tight schedule and weather. TC set up for 12/16/02 at 12:30 PM.
13-Dec-02	Agency Contact Report	Status of Action Letter and teleconference set-up with Agency e-mails
16-Dec-02	Fax	Fax to FDA regarding TC for 12/18/02 to discuss status of action letter for SPIRIVA
16-Dec-02	Agency Contact Report	FDA indicated letter being circulated among disciplines. Labeling issues being addressed at Chowdhury's request. Telecon set for Wed., December 18 at 11:30 AM to FDA to update status.
16-Dec-02	Agency Contact Report	e-mails to Agency referencing toxicology issues in an overview by Neil Johnson and a discussion of the values included in the summary version" of Nov. 19 submission"
18-Dec-02	Agency Contact Report	FDA teleconference discussing that the action letter is now with Dr. Meyer for review. No date for sending. Dr. Blank wants to talk to Dr. Meyer if expected to be after Christmas. BIPI upset by lateness.
19-Dec-02	Agency Contact Report	FDA Zeccola said action letter to come before Christmas 2002. Either on 12/23 evening or 12/24 morning e-mailed to Peter by PDF and faxed to BIPI. Peter will distribute.
20-Dec-02	FDA General Regulatory Letter	FDA approvable letter 12-20-02 for SPIRIVA

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23-Dec-02	General Correspondence	Response to FDA Approvable Letter: Letter of Intent to File an amendment
14-Jan-03	Agency Contact Report	e-mail to Agency requesting informal meeting to discuss items in Action letter and what is needed for approval of application
17-Jan-03	Amendment to Unapproved NDA, Meeting with Health Authority Corresp - Fax	FAX - BIPI requesting a meeting regarding clarification on CMC comments contained in Approval Letter dated December 20, 2002
17-Jan-03	Amendment to Unapproved NDA, Meeting with Health Authority Corresp	BIPI requesting a meeting regarding clarification on CMC comments contained in the Approval Letter of December 20, 2002
27-Jan-03	General Correspondence	Meeting Participants and Clarification Point Correction contained in Point 9. CMC Meeting set for January 31, 2003
27-Jan-03	Fax	Fax sent to FDA providing BI's participants for CMC Meeting January 31, 2003. Clarification re Point 9 of CMC Discussion Points for Clarification
4-Feb-03	Agency Contact Report	E-mail to FDA Zeccola regarding clarification on promotional material, safety update, and toxicology clarification for labeling.
25-Feb-03	General Correspondence, Response to FDA Comments or Request for Information, Meeting with Health Authority Corresp	CMC Clarification Meeting Minutes - RJR - meeting on January 31, 2003
25-Feb-03	Response to FDA Comments or Request for Information	Meeting minutes; response to FDA request for information - reference to CMC meeting of January 31, 2003
25-Feb-03	Agency Contact Report	e-mails to FDA regarding feedback to Action Letter issues: labeling, toxicology, dose calculations, safety update
27-Feb-03	Agency Contact Report	e-mails regarding SPIRIVA pending FDA issues i.e. promotional material, safety update, toxicology
14-Mar-03	Agency Contact Report	FDA telecon on 3-28-03 to discuss pre-clinical toxicology issues
14-Mar-03	Meeting with Health Authority Corresp	Confirm telephone Conference call between FDA and BI to review specific NDA issues related to pre-clinical toxicology
20-Mar-03	Agency Contact Report	ACR FDA agrees to approve 1-3-5 packaging and wants BI to develop improved packaging for later use
24-Mar-03	Agency Contact Report	In use study with 1-3-5 not required. 3 mth stability for 1-3-5 to be filed 1 mth after BI completes response to approvable letter. 6 mth report due 3 mths later. In 2-3 mths FDA requests update of optimized packaging and overall timeline.
25-Mar-03	Meeting with Health Authority Corresp	FDA telecon mtg minutes with BIPI on March 20th to discuss BI's Feb 25th submission of configuration of internal packaging of Tio capsules. FDA stating that 3 capsules per blister card is not optimal. FDA proposed BI to conduct an in-use stability study
31-Mar-03	Agency Contact Report	e-mail regarding rescheduling of telecon with FDA from March 28 to April 1 at 9:00 AM to discuss toxicology issues.
1-Apr-03	Agency Contact Report	April 1, 2003 teleconference with FDA to discuss toxicology, promotional material and safety update issues and decisions made.
7-Apr-03	General Correspondence	FDA fax with minutes of March 24, 2003 TC discussing 1-3-5 blister pack and stability data to support it.

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7-Apr-03	Fax	Fax from FDA with minutes regarding April 1, 2003 TC discussing dose ratios of tio between animals and humans and degradation products in the drug substance and drug product.
23-Apr-03	Agency Contact Report	Discussion with FDA for combining AE reports and asking for feedback on Holter Study with additional e-mails attached.
17-Jun-03	Agency Contact Report	DDMAC information on pre-clearance promotional material prior to NDA approval relating to SPIRIVA and other drugs
28-Jul-03	Agency Contact Report	E-mail to FDA of cover letter from Response Package being submitted on 7-31-03. Response to December 20, 2002 Action Letter.
31-Jul-03	Response to FDA Comments or Request for Information, Health Auth Comments CMC, Health Auth Comments Labeling, Health Auth Comments Pharm Tox	COMPLETE Response to FDA Action Letter dated December 20, 2002
31-Jul-03	Health Auth Comments CMC, Response to FDA Comments or Request for Information Field Copy	Field Copy of BIPI CMC Response to Approvable Letter of December 20, 2002 (volumes 2 - 4)
31-Jul-03	Response to FDA Comments or Request for Information, Health Auth Comments CMC, Health Auth Comments Labeling, Health Auth Comments Pharm Tox	COMPLETE Response to FDA Action Letter dated December 20, 2002
8-Aug-03	Amendment to Unapproved NDA	REPLACEMENT of Cover Letter to Complete Response to FDA Action Letter of December 20, 2002
11-Aug-03	Agency Contact Report	ACR with e-mail sent to BI and BIPI individuals regarding complete response package submission and cover letter. A formal meeting request is made for October. Discussions to be held 3rd and 4th week in August.
22-Aug-03	Amendment to Unapproved NDA, Health Auth Comments CMC Field Copy	Stability Report
22-Aug-03	Health Auth Comments CMC	This amendment provides for updated stability data (3 months in the Wannenblister 3 count configuration). Reports H008223 and H008221 were submitted. This was a complete electronic submission.
25-Aug-03	Agency Contact Report	Discussion with FDA regarding 3-month stability submission on August 22 and the need for a letter acknowledging the complete response package submission sent on July 31st that should have been sent on August 15th
26-Aug-03	FDA Acknowledgment of Receipt	FDA letter acknowledging receipt on 8/1/03 or 7/31/03 resubmission to NDA. Complete Class 2 Response to 12/12/02 Action letter. User fee goal is 2/1/04.
26-Aug-03	FDA Acknowledgment of Receipt - Fax	Fax from FDA acknowledging receipt of complete response package sent on July 31, 2003
26-Aug-03	Agency Contact Report	Complete response submission letter signed and to be sent today or tomorrow. FDA to work with BI as requested
12-Sep-03	Agency Contact Report	discussion with FDA on status of complete response review and schedule for feedback on labeling

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24-Oct-03	Response to FDA Comments or Request for Information, Health Auth Comments Labeling	Actual 1:1 scale 1-3-5 blister label drawings for SPIRIVA capsules to be used for the market. Box of six placebo 1-3-5 blister cards without current proposed labeling.
27-Oct-03	Agency Contact Report	Discussion with Dr. Chowdhury regarding NDA review and labeling decisions. Agreed to teleconference with BIPI Management.
28-Oct-03	Agency Contact Report	Discussion between BIPI and Dr. Chowdhury regarding status of NDA review, CMC review, and possibility of two cycle approval
5-Nov-03	Amendment to Unapproved NDA, Health Auth Comments CMC	Updated CMC Stability Report
5-Nov-03	Amendment to Unapproved NDA, Health Auth Comments CMC Field Copy	CMC Amendment / Updated Stability Report H008330 and H008331
7-Nov-03	Health Auth Comments CMC	FDA CMC IR Letter with 26 questions
7-Nov-03	Health Auth Comments CMC, Health Auth Comments Labeling	FDA IR Letter regarding CMC and Labeling
12-Nov-03	Agency Contact Report	ACR with e-mail from Tony Zeccola indicating that a discussion may be held with Dr. Schroeder once BIPI has indicated a timeframe and a copy of the CMC IR Letter received on November 7, 2003
13-Nov-03	General Correspondence, Health Auth Comments CMC	BIPI requesting a telephone conference with CMC Reviewer to discuss several comments where clarification is required. Reference is made of Information Request Letter dated November 7, 2003
13-Nov-03	General Correspondence, Health Auth Comments CMC - Fax	FAX - BIPI request for telephone conference for clarification to Information Request dated November 7, 2003
18-Nov-03	Health Auth Comments CMC	FDA fax requesting additional CMC information for the November 20, 2003 face-to-face meeting
20-Nov-03	Agency Contact Report	ACR regarding meeting between FDA chemists and BI tech and regulatory team regarding clarification in the IR letter of November 7, 2003 to discuss CMC and labeling issues.
30-Nov-03	Health Auth Comments CMC - Fax	FDA Fax regarding C of A for foil and question for study 205.131
4-Dec-03	Response to FDA Comments or Request for Information, Health Auth Comments CMC	Response to FDA Request for Information dated November 7, 2003 and November 18, 2003 Fax
5-Dec-03	Health Auth Comments CMC, Response to FDA Comments or Request for Information Field Copy	FIELD COPY of BIPI's Response to FDA Request for Information November 6th Letter and November 18th Fax
10-Dec-03	Health Auth Comments CMC	FDA e-mail letter with 6 CMC questions and 26 Labeling CMC questions
10-Dec-03	Health Auth Comments CMC, Health Auth Comments Labeling	FDA official letter with 6 CMC questions and 20 Labeling questions.
11-Dec-03	Response to FDA Comments or Request for Information, Health Auth Comments Clin PK	Response to FDA Request for Information of November 28, 2003
13-Dec-03	Fax	FDA Fax regarding new container closure system

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16-Dec-03	Labeling	Revised Labeling submitted in response to FDA's November 07, 2003 CMC Information Request Letter. Other outstanding modifications also incorporated into labeling.
16-Dec-03	Response to FDA Comments or Request for Information, Health Auth Comments CMC Field Copy	Field Copy of Submission #29 BIPI Response to FDA Information Request Letter of December 10, 2003
16-Dec-03	Health Auth Comments Labeling, Health Auth Comments CMC	BIPI's complete response to FDA Information Request Letter of December 10, 2003. Labeling amendment to respond to FDA's Information Request Letters of November 07, 2003 (comments 12, 20, 21, 22 and 25) and December 10, 2003.
18-Dec-03	Response to FDA Comments or Request for Information	BI's response to FDA's 15Dec03 telephone information request for labeling was provided. The value of 32.357 mg/kg in mice is correct.
19-Dec-03	Health Auth Comments CMC	FDA CMC questions and comments based on the November 7 and December 4 submissions
23-Dec-03	Health Auth Comments Labeling	Preliminary questions on labeling (Clinical and CMC) - 19 questions
23-Dec-03	Health Auth Comments Clin PK Fax	FDA Fax requesting clinical data
30-Dec-03	Response to FDA Comments or Request for Information, Labeling	Response to FDA Labeling Comments and Information Requests of December 23, 2003
30-Dec-03	Agency Contact Report	E-mail to Tony Zeccola of submission being sent out on 12-30-03 with attachments containing items being submitted to FDA of cover letter, response to labeling and clinical IR along with <u>annotated and clean draft of labeling</u>
5-Jan-04	Response to FDA Comments or Request for Information, Health Auth Comments CMC Field Copy	FIELD COPY - COMPLETE Response to FDA Information Requests of December 19, 2003 and December 23, 2003
5-Jan-04	Health Auth Comments CMC, Response to FDA Comments or Request for Information	COMPLETE Response to FDA CMC Information Request of December 19, 2003 and December 23, 2003
8-Jan-04	General Correspondence	An email was sent to the FDA Project Manager, Tony Zeccola, to inform him of the January 8th labeling submission. The signed cover letter for the January 8th submission was included as an attachment.
8-Jan-04	General Correspondence	Email was received from FDA confirming they would be on the look out for the January 8, 2004 labeling amendment.
8-Jan-04	Labeling, Health Auth Comments Labeling	Labeling Amendment to revise and update the Patient Instructions for Use, cartons, foils and HandiHaler to be consistent with 30Dec03 version of the Package Insert which takes into account FDA's 23Dec03 comments.
13-Jan-04	Agency Contact Report	FDA telecon to discuss Clinical and Pharm/Tox and CMC issues between the BI Spiriva Team and management and FDA
14-Jan-04	Amendment to Unapproved NDA, Labeling	A labeling amendment for the package insert and the patient's instructions for use was made in accordance with the 13Jan04 tcon with FDA. This was a complete electronic submission.

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14-Jan-04	Health Auth Comments CMC	FDA CMC Fax discussing cleanliness, hygiene, and defects of manufacturing, functional and assembly which are part of the HandiHaler specs provided in December 4, 2003 amendment and January 5, 2004 amendment. Request to modify wording.
15-Jan-04	Response to FDA Comments or Request for Information, Health Auth Comments CMC	Response to FDA Request for Information Fax 2004-01-14. Updated specification sheet Drug Product - degradant BIIS 56 SE to QC Testing Spec for DP and proposed a shelf-life acceptance criterion of <0.5%
15-Jan-04	General Correspondence	Reference to January 13, 2004 telephone conference with FDA re clinical postapproval commitment and options to qualify selected degradation products.
15-Jan-04	Response to FDA Comments or Request for Information, Health Auth Comments CMC Field Copy	FIELD COPY to Complete Response to CMC IR of January 14, 2004 and CMC Commitment of January 13, 2004
15-Jan-04	Agency Contact Report	e-mails between BI and FDA regarding BI's commitment to clinical, toxicology, and CMC as discussed in 1/13/04 teleconference. Commitment attached to ACR and e-mails.
22-Jan-04	Response to FDA Comments or Request for Information, Health Auth Comments Clin PK	Response to FDA e-mail January 19, 2004 for all US and international SPIRIVA studies for which a report is completed
22-Jan-04	Health Auth Comments Labeling, Amendment to Unapproved NDA	BI submitted a labeling amendment in response to FDA's 22Jan04 email with labeling changes. The Package Insert and Patient's Instructions for Use were submitted in complete electronic format.
26-Jan-04	Amendment to Unapproved NDA, Labeling	Labeling Amendment - Patient Instruction and Package Insert
26-Jan-04	Agency Contact Report	ACR of FDA request for safety update tables from clinical trials referencing 282 deaths, unrelated to tiotropium bromide. Drs. Blank and Kaplan participated in discussion along with Peter Fernandes. Subsequent e-mail to Tony Zeccola along with table inc
30-Jan-04	FDA NDA Action Letter	FDA FAX - Spiriva Approval Letter
30-Jan-04	FDA NDA Action Letter	Official Approval Letter from FDA